Endpoints in clinical trials of fluid resuscitation of patients with traumatic injuries

Charles E. Wade and John B. Holcomb

Trauma is a worldwide problem with severe and extensive consequences impacting individuals and society as a whole.[1] Death due to traumatic injuries is the leading cause of death of individuals between the ages of 1 and 44 years. Hemorrhage is a major contributor to the predicament of traumatic injury and care. The initial treatment of patients with traumatic injuries who are hypotensive because of hemorrhage is believed to be paramount to their survival. After assuring adequate respiration and control of bleeding, early resuscitation with fluids has been advocated for victims of traumatic injuries.[2] The goal of fluid intervention is to replace the volume of blood lost during hemorrhage, thus increasing oxygen delivery to the tissues and ultimately improving survival.[1] In addition, adequate fluid resuscitation is postulated to reduce the incidence of secondary complications such as acute respiratory failure, renal failure, and infection. Of the fluids used presently for the resuscitation of hypotensive trauma victims, however, none has been demonstrated to improve survival or decrease the incidence of secondary complications. Solutions have been approved for other clinical indications and then applied to care of the trauma patient. The absence of validation of the indication of these fluids in patients with traumatic injuries is due to a number of factors, including the heterogeneity of the trauma patient population and the focus on near-term resuscitation endpoints rather than endpoints related to clinical outcome.

ABBREVIATIONS: AIS = anatomical injury score; DCLHb = diasprin cross-linked hemoglobin; GCS = Glasgow Coma Scale; HSD = hypertonic saline dextran; MOD = multiple organ dysfunction; SOC = standard of care.

From the US Army Institute of Surgical Research, Fort Sam Houston, Texas.

Address reprint requests to: Charles E. Wade, PhD, US Army Institute of Surgical Research, 3400 Rawley E Chambers Avenue, Fort Sam Houston, TX 78234-6315; e-mail: charles.wade@cen.amedd.army.mil.

doi: 10.1111/j.1537-2995.2005.00156.x

TRANSFUSION 45;S1:4S-8S.

POPULATION HETEROGENEITY

The study of resuscitation of trauma victims is confounded by a variety of factors, especially when treatment is initiated in the field at the site of the accident. The first confounding factor is diagnosis of the cause, type, and magnitude of the injuries. The cause of injury is often varied (gunshot, stabbing, car accident, or fall), as are the resultant injuries (blunt or penetrating). In the field, the determination of simple variables, including blood pressure, respiratory rate, pulse rate, and cognitive function, is used to evaluate the patient.[2] Diagnosis of the extent of injury, such as brain damage or volume of internal bleeding, is delayed until a definitive diagnosis is made in the hospital, well after the initial administration of resuscitation solutions. Therefore, the criteria for enrollment of a specific patient population to reduce variability are difficult to define.

In a recent clinical trial of diasprin cross-linked hemoglobin (DCLHb), randomization of the patients led to an unequal assignment that adversely impacted outcome survival. The incidence of major head injury, defined by a Glasgow Coma Scale (GCS) score of 3, was 18 percent (11/58) for standard of care (SOC) and 38 percent (20/53) for the treatment group.[3] Patients with traumatic brain injury and hypotension have a poor prognosis,[4] but to definitively rule in or out the possibility of traumatic brain injury in the field is typically beyond the capabilities of most emergency medical systems. In addition, those patients randomized to the treatment arm had a 13 percent (7/53) incidence of cardiac arrest requiring cardiopulmonary resuscitation compared to a rate of 2 percent (1/58) for those enrolled for the SOC. Thus, the inherent heterogeneity of the population and entry criteria that allowed this unequal distribution led to assignment of a greater number of subjects to the treatment arm with the probability of a poorer outcome. This resulted in early termination of the study by the sponsor. In a concurrent study in Europe, the distribution of the patients between groups was better matched.[5] In those patients receiving DCLHb, there was no difference in mortality compared to SOC; however, there was a trend toward a reduction in the number patients requiring blood products, a primary endpoint of the study.

Report Documentation Page

Form Approved
OMB No. 0704-0188

Public reporting burden for the collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington VA 22202-4302 Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to a penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
01 JUL 2005	**N/A**	**-**

4. TITLE AND SUBTITLE	
Endpoints in clinical trials of fluid resuscitation of patients with traumatic injuries	5a. CONTRACT NUMBER
	5b. GRANT NUMBER
	5c. PROGRAM ELEMENT NUMBER
6. AUTHOR(S)	5d. PROJECT NUMBER
Wade C. E., Holcomb J. B.,	5e. TASK NUMBER
	5f. WORK UNIT NUMBER
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) **United States Army Institute of Surgical Research, JBSA Fort Sam houston, TX 78234**	8. PERFORMING ORGANIZATION REPORT NUMBER
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)	10. SPONSOR/MONITOR'S ACRONYM(S)
	11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release, distribution unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a REPORT	b ABSTRACT	c THIS PAGE			
unclassified	**unclassified**	**unclassified**	**SAR**	**5**	

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std Z39-18

Of the studies of hypertonic saline dextran (HSD), there is only one that has not shown a trend toward an improvement in outcome.[6] Further review of this study revealed that a larger portion of the patients randomly assigned to the HSD group (30%) had no obtainable pulse compared to 18 percent in the SOC group.[7] Furthermore, in the HSD subjects, 30 percent had a GCS score of 8 or less, with 13 percent having an anatomical injury score (AIS) for the head region of 4 or greater. In contrast, in the SOC group only 6 percent had an AIS of 4 or greater and there were 17 percent with a GCS of 8 or less. In the HSD population, there were three patients with an injury severity score of 75, whereas none were reported in the SOC group. Based on the Trauma and Injury Severity Score of the HSD group, 19 percent of the population had a probability of survival of 25 percent or less, in contrast to 11 percent in the SOC patients. Thus, during randomization, based on a number of measures, the HSD treatment group was assigned patients with a lower probability of surviving. Although randomization is desired, the enrollment of patients with traumatic injuries at the onset of treatment may lead to an unequal distribution between groups of patients owing to the variety of injury modes and magnitude affecting overall morbidity and mortality.[8] Entry criteria must be established that exclude from the study those patients with a high likelihood of dying.

The complexity of care is also a confounding factor. Many of these patients are in the hospital for weeks with a diverse set of complications treated with varying approaches that can influence outcome. For example, after completion of resuscitation with an experimental solution, the selection of follow-on fluids has been inconsistent. In a multicenter study, after the administration of the test solutions, patients were subsequently resuscitated with Ringer's lactate, normal saline, or Plasmalyte A (Baxter Healthcare, Deerfield, IL) because these fluids are part of the SOC at specific institutions. Although the different solutions may make no clinical difference, it is an example of the variance across centers. Ongoing studies, such as those funded as Glue Grants by the National Institute of General Medical Sciences (a component of the National Institutes of Health), have established specific uniform procedures for all centers enrolling patients to deal with the issue of treatment variability (http://www.gluegrant.org/clinical-protocols.htm).

The use of multiple centers also contributes to study variability. For example, the distribution of patients on factors such as injury type is variable. In one multicenter study, injury due to blunt trauma was 12 percent at one of the centers and 43 percent at another center.[9] Another issue is comparison across countries. In the US trial of DCLHb, 48 percent of the subjects had penetrating injuries in contrast to the European study with an incidence of 30 percent.[3,5] Between centers, variability may be an additional confounding factor. In terms of subsequent clinical application, multiple center variability does increase application of the findings to a wider patient population and expand use by diverse medical facilities.

Thus, in the study of resuscitation solutions in trauma, there is a diverse patient population and varied care between institutions and among a myriad of physicians, all contributing to a large variance in the population. To overcome the diversity of the patient population, large sample sizes are required. For example, given a mortality rate of the order of 20 percent in patients with a systolic blood pressure of less than 90 mmHg,[6] to demonstrate a 3 to 5 percent improvement in survival would require a study population of more than 5000 patients.[8]

RESUSCITATION ENDPOINTS

Resuscitation endpoints must be delineated from clinical endpoints. A wide range of physiologic endpoints have been advocated for assessing the adequacy of resuscitation.[10] Resuscitation endpoints (physiologic measures) are used extensively in evaluating the efficacy of solutions; however, these physiologic endpoints have not been associated directly with clinical outcome. A classic example is systolic blood pressure. Although it is recommended that patients be resuscitated to a systolic blood pressure of 90 mmHg in the field, there are no data supporting the efficacy of this procedure on subsequent morbidity or long-term survival.[2,11] In fact, there are studies suggesting that the elevation of systolic blood pressure in patients with traumatic injuries may be detrimental.[12] Other studies, however, have failed to demonstrate the efficacy of hypotensive resuscitation.[13] At present, resuscitation criteria have been deemed surrogate endpoints that may suggest improvement in clinical endpoints. Efforts should be directed at validating these endpoints as to clinical efficacy. Until this validation is accomplished, the use of resuscitation endpoints will not be accepted as evidence for regulatory approval of resuscitation solutions.

CLINICAL ENDPOINTS

The present criteria to evaluate the efficacy of resuscitation solutions are based on definitive influence on clinical outcome. The presently accepted criteria are an improvement in survival, a reduction in morbidity, specifically a decrease in the incidence of multiple organ failure, or a reduction in the number of patients requiring allogeneic blood transfusions.

Mortality

The use of an increase in long-term survival (>28 days) has been readily accepted as it is: an outcome understood by everyone, an important clinical endpoint, a clear objective criterion, and one that is accepted by regulatory agencies.

Although clear as an objective, increasing survival has yet to be demonstrated for regulatory approval of a resuscitation fluid. The reasons for this are based on the demographics of trauma. First, the causes of death are multiple. Patients may die for different reasons, even though the cause of injury is similar. For example, the cause of death in trauma patients in a study of resuscitation solutions was varied: injury of the central nervous system (33%), hemorrhage (46%), and multiple organ failure (21%).[14] Variation in the cause of death could lead to difficulty in demonstrating the efficacy of a solution. The etiology of death is very different and may require unique solutions for each cause and thus unique trials to demonstrate efficacy.

Second, death may occur early or late. In the case of late deaths, the complexity of care and variations in treatment days after administration of the experimental resuscitation solution at the time of initial care could be contributing factors. In the US trial of HSD, 250 mL of test solution was administered in the field with various standards of care thereafter.[9] No care was withheld; therefore, the efficacy of the solution was evaluated in the presence of multiple standards of care. There was a pronounced mortality in the first hours after injury with a tailing off over the following 48 hours. The difference in survival appeared to be in this later period. Thus, the timing of the effect of interventions has been evaluated. These include survival to hospital admission and 24-hour survival. The regulatory approach has remained the assessment of long-term survival, however. This has been difficult in the study of trauma patients owing to the fact that some are discharged against medical advice or transferred to other hospitals, and subsequently there is no follow-up. In most studies an assumption is made that if patients are not readmitted to the hospital, they have survived.

Finally, variation in the severity of injury and the prognosis of the individual patient are confounding factors. In the trauma population there is a limited number of patients that can benefit from an intervention. There are, basically, three populations enrolled in studies of trauma patients. The first population, the majority of patients, will live irrespective of the treatment. Studies have tried to exclude this population by using inclusion criteria such as a systolic blood pressure of less than 90 mmHg. The second population will die irrespective of the treatment. Exclusion criteria such as asystole (systolic blood pressure, <50 mmHg) have been tried to define this population. With these types of inclusion and exclusion criteria in severely injured trauma victims, more than 55 percent of the population had a more than 95 percent probability of survival and more than 15 percent had a more than 25 percent probability of dying.[7,8] Therefore, the remaining 30 percent of the patients constitute the population in which efficacy of a solution can be evaluated. Ongoing studies have excluded patients who require cardiopulmonary resuscitation, emergency thoracotomy, or correction of severe base deficits. These studies have also added the inclusion criteria of ongoing blood transfusions and moderate base deficit in an attempt to further narrow the population that may benefit from new interventions. A priori definition of the population of trauma patients that will benefit from a treatment, though difficult,[8] has been successful in some cases. In early studies to define head trauma, a GCS score of 8 or less was used. Employing this criterion resulted in a 50 percent false-positive rate and a 50 percent false-negative rate, in hypotensive patients with traumatic injuries.[15] In a recent study by Cooper and coworkers,[16] the entry criteria were similar; however, they focused on “severe” head trauma attributed to blunt injury. This resulted in a significant increase in the percentage of patients subsequently diagnosed with traumatic brain injury (mean AIS for the head region of 4 or greater). Thus, by a priori training of emergency personnel to recognize the injury and identify the patient population, the efficacy of the solutions can be evaluated.

Although an increase in survival is a clear-cut and uniformly acceptable endpoint for the efficacy of a resuscitation solution, it has been difficult to demonstrate. A question that should be raised is: With all of the divergent medical interventions in the course of care of a trauma victim, why should administration of fluid at the onset of care be expected to impact survival 28 days later? Although it is readily agreed that long-term survival is the ultimate goal, the probability of a solution administered at the onset of treatment showing a positive effect on mortality with extensive clinical interventions over a 10-day intensive care unit stay is a difficult hurdle. This should be considered in the design of trials; specifically they should be powered adequately to achieve the endpoint of improved survival.

In the evaluation of the efficacy of resuscitation solutions based on an increase in survival, an additional measure should be recorded: the quality of life of the patients who are saved. This was addressed by Vassar and associates[14] in a study on the effects of resuscitation with hypertonic solutions in patients with head injuries. There was a trend for an improvement in survival in this subpopulation. More interesting, however, was the observation of an improvement in the Glasgow Outcome Score, a measure of neurologic function, and thus quality of life, in those patients who survived who had been treated with hypertonic solutions. This observation was followed by a more extensive study by Cooper and associates.[16] Hypertonic saline administered to patients with traumatic brain injuries and hypotension resulted in no improvement in neurological function as measured by Glasgow Outcome Score. Thus, the issue of quality of life should be addressed concurrently with survival.

Morbidity

The incidence of multiple organ dysfunction (MOD) is high in patients with severe traumatic injuries and associated with a poor rate of survival. In the past, use of these medical complications as endpoints was hampered by the lack of uniformity of the diagnosis. Now, however, with the establishment of set criteria for diagnosis, they have become useful endpoints to assess the efficacy of a treatment. Contributing factors to MOD are respiratory failure, renal failure, liver failure, cardiovascular dysfunction, neurologic impairment, and infection.[17] Physiologic measures of the magnitude of dysfunction of these systems have been entered into the MOD score providing a metric for assessing morbidity.[17] Interest in the condition of these organ systems is not limited only to their contribution to mortality, but also to economic issues. Patients who develop these conditions have increased intensive care unit length of stay and increased incidence of delayed mortality; both are associated with an increase in cost. A reduction in the incidence of MOD has been accepted as a primary endpoint by some regulatory agencies, but has had limited application in the evaluation of resuscitation solutions in trauma patients. The incidence of MOD has been reported in the study of fluids in the treatment of trauma patients For example in the US trial of HSD, the incidence rate of "postadmission medical complications" was 6 percent (13/211) for SOC and 3 percent (7/211) for those patients treated with HSD.[9] Furthermore, there were no patients with MOD in the HSD group. Although these data were favorable, postadmission complications were treated as secondary endpoints and the study was not powered to attain significance. In the US and European trials of DCLHb, a reduction of early organ failure was a primary endpoint.[3,5] In the US trial, the multiorgan dysfunction score was increased significantly in the group receiving DCLHb.[3] As noted above, however, the randomization of patients with a high probability of dying was skewed to treatment with DCLHb. In the European trial, the group assignments were better matched, and there was no difference in MOD score between treatments.[5] With acceptance of uniform diagnoses of postadmission complications and validated scoring systems, the reduction of organ dysfunction has become a viable endpoint to assess the efficacy of fluids in the resuscitation of trauma patients.

Use of blood products

A reduction in the number of patients requiring allogeneic transfusions is a relatively recent endpoint of studies of resuscitation solutions in trauma patients. Acceptance of this endpoint is based on recognition that transfusions carry inherent risks such as the possibility of infection, immunosuppression, and adverse effects on the microcirculation. Although transfusion has been established as a predictor of survival in studies of patients with traumatic injuries, a causal relationship has yet to be demonstrated.[18] Because of the demonstrated risks, however, avoidance of transfusion of allogeneic blood has been used as an endpoint. In the European study of DCLHb, there was a decrease in the number of patients requiring blood transfusions from 58 percent (37/53) for those treated with DCLHb compared to 82 percent (51/62) for SOC.[5] Although favorable, a significant difference in the number of patients requiring blood transfusions was not demonstrated. In studies of HSD, no effect on the number of patients requiring transfusions has been demonstrated.[19,20] At present, a reduction in the number of patients requiring blood transfusions has not been demonstrated for a fluid evaluated in the field for the treatment of the patient with traumatic injuries.

The quantity of blood products used has been considered a surrogate endpoint. There was a significant reduction in the volume of blood products used in the immediate postadmission period in patients administered DCLHb in the European trial.[5] It has been suggested that administration of HSD in the field can result in a decrease in blood product requirements.[20] The use of the volume of blood products required as a surrogate is associated with the increase in mortality observed as the use of blood is increased and is correlated with increased morbidity. As with the absolute avoidance of transfusion, however, the quantity of blood products used has not been demonstrated to have a direct causal relationship with mortality or morbidity.

SUMMARY

Evaluation of fluids in the resuscitation of the patient with traumatic injuries is confounded by a variety of factors. The demographics are diverse, treatment is initiated in a limited diagnostic environment, and the follow on care is varied and complex. The ability to isolate the population that will benefit from a specific fluid treatment is difficult. These limitations can be overcome by enrollment of a large number of patients. This instills an increase in variability because multiple centers must be enrolled, however, further confounding the analysis.

The selection of an endpoint must be based on an improvement in clinical outcome. A variety of resuscitation endpoints are used, but they have not been associated directly with an improvement in clinical outcome. These surrogate endpoints must be investigated, and their relationship to an improvement in the clinical course of the patient must be demonstrated. At present, the primary clinical endpoint in the evaluation of a resuscitation solution in the care of the trauma patient is an increase in survival. When improved survival is the endpoint, the quality of life of those who survive should also be considered. Other accepted endpoints are a reduction in the inci-

dence of organ failure and the avoidance of allogeneic blood transfusions. At present, no solution for the resuscitation of the trauma patient has been approved by a regulatory agency employing these criteria. Studies are necessary and should be powered adequately to account for the diversity and the complexity of the population of patients with traumatic injuries.

REFERENCES

1. Moore FA, McKinley BA, Moore EE. The next generation in shock resuscitation. Lancet 2004;363:1988-96.
2. Trauma ACoSCo. Advanced trauma life support course: instructors manual. Chicago: American College of Surgeons; 1994.
3. Sloan EP, Koenigsberg M, Brunett PH, et al. Post hoc mortality analysis of the efficacy trial of diaspirin cross-linked hemoglobin in the treatment of severe traumatic hemorrhagic shock. J Trauma 2002;52:887-95.
4. Chesnut RM, Marshall SB, Piek J, et al. Early and late systemic hypotension as a frequent and fundamental source of cerebral ischemia following severe brain injury in the Traumatic Coma Data Bank. Acta Neurochir Suppl (Wien) 1993;59:121-5.
5. Kerner T, Ahlers O, Veit S, et al. DCL-Hb for trauma patients with severe hemorrhagic shock: the European "On-Scene" multicenter study. Intensive Care Med 2003;29:378-85.
6. Wade CE, Kramer GC, Grady JJ, et al. Efficacy of hypertonic 7.5% saline and 6% dextran-70 in treating trauma: a meta-analysis of controlled clinical studies. Surgery 1997;122:609-16.
7. Vassar MJ, Perry CA, Holcroft JW. Prehospital resuscitation of hypotensive trauma patients with 7.5% NaCl versus 7.5% NaCl with added dextran: a controlled trial. J Trauma 1993;34:622-32; discussion 32-3.
8. Riou B, Landais P, Vivien B, et al. Distribution of the probability of survival is a strategic issue for randomized trials in critically ill patients. Anesthesiology 2001;95:56-63.
9. Mattox KL, Maningas PA, Moore EE, et al. Prehospital hypertonic saline/dextran infusion for post-traumatic hypotension. The U.S.A. Multicenter Trial. Ann Surg 1991;213:482-91.
10. Tisherman SA, Barie P, Bokhari F, et al. Clinical practice guideline: endpoints of resuscitation. J Trauma 2004;57:898-912.
11. Kaweski SM, Sise MJ, Virgilio RW. The effect of prehospital fluids on survival in trauma patients. J Trauma 1990;30:1215-8; discussion 8-9.
12. Bickell WH, Wall MJ Jr, Pepe PE, et al. Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. N Engl J Med 1994;331:1105-9.
13. Dutton RP, Mackenzie CF, Scalea TM. Hypotensive resuscitation during active hemorrhage: impact on in-hospital mortality. J Trauma 2002;52:1141-6.
14. Vassar MJ, Perry CA, Gannaway WL, Holcroft JW. 7.5% sodium chloride/dextran for resuscitation of trauma patients undergoing helicopter transport. Arch Surg 1991;126:1065-72.
15. Wade CE, Grady JJ, Kramer GC, et al. Individual patient cohort analysis of the efficacy of hypertonic saline/dextran in patients with traumatic brain injury and hypotension. J Trauma 1997;42(5 Suppl):S61-5.
16. Cooper DJ, Myles PS, McDermott FT, et al. Prehospital hypertonic saline resuscitation of patients with hypotension and severe traumatic brain injury: a randomized controlled trial. JAMA 2004;291:1350-7.
17. Marshall JC, Cook DJ, Christou NV, et al. Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. Crit Care Med 1995;23:1638-52.
18. Malone DL, Dunne J, Tracy JK, et al. Blood transfusion, independent of shock severity, is associated with worse outcome in trauma. J Trauma 2003;54:898-905; discussion 905-7.
19. Younes RN, Aun F, Ching CT, et al. Prognostic factors to predict outcome following the administration of hypertonic/hyperoncotic solution in hypovolemic patients. Shock 1997;7:79-83.
20. Maningas PA, Mattox KL, Pepe PE, et al. Hypertonic saline-dextran solutions for the prehospital management of traumatic hypotension. Am J Surg 1989;157:528-33; discussion 33-4.